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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
GODDARD, LAURA B

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/994,068	ARAKAWA ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-24,29,30,42 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-24,29,30,42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/2/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed February 2, 2006 in response to the Office Action of September 22, 2005, is acknowledged and has been entered. Previously pending claim 19 has been amended. Claims 19-24, 29, 30, 42 and 43 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

3. Claims 19-24, 29, 30, 42, and 43 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for **a method for treating cancer comprising administering mAb74 or fragment thereof to induce apoptosis in Her2 overexpressing cells in cell culture (*in vitro*)**, does not reasonably provide enablement for **a method for treating cancer in a patient comprising administering an antibody or fragment thereof that binds HER2 and induces apoptosis in Her2 overexpressing cells *in vivo***. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims (see the Office Action of September 22, 2005, section 5, p. 9-15).

Applicants amended claim 19 to define the antibody as binding to HER2. Claims 19-23, 29, and 30 are broadly drawn to the treatment of cancer characterized by overexpression of HER2 in a patient comprising administering **any** antibody or fragment

thereof that binds HER2 and induces apoptosis in HER2 overexpressing cells. Claims 24, 42 and 43 are drawn to the treatment of cancer characterized by overexpression of HER2 in a patient comprising administering an antibody produced by hybridoma cell line ATCC No. 12078 or an antibody that binds to an epitope on HER2 which is recognized by a monoclonal antibody produced by hybridoma cell line ATCC No. 12078. All claims are still drawn to the treatment of patients *in vivo*, although the specification is enabling for *in vitro*.

4. Applicants argue that predictability alone is not the standard for enablement, rather the standard for enablement is whether one skilled in the art could practice the claimed invention without undue experimentation and Applicants assert that the specification enables a person skilled in the art to practice the claimed invention without undue experimentation. Applicants point to the specification for teaching how to make antibodies that bind HER2 (Example 2), how to select an antibody that induces apoptosis in HER2 overexpressing cells (Example 6), how to make pharmaceutical compositions comprising an antibody that binds HER2 and induces apoptosis in HER2 overexpressing cells (p. 12 of specification), and routes for administration for such pharmaceutical compositions (p. 11 of specification) (see p. 14-15 of the Amendment filed February 2, 2006).

The argument has been considered but is not found persuasive because Applicants have only enabled the induction of apoptosis in HER2 overexpressing cells comprising administering the antibody mAb74, produced by hybridoma cell line ATCC

No. 12078, which binds to HER2, in cell culture (*in vitro*). Examiner has inserted the *Wands* factors below:

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification does not provide guidance or examples for treating cancer **in a patient** comprising administering **any** antibody that binds HER2 and induces apoptosis or an antibody that binds to the same epitope as mAb74, produced by hybridoma cell line ATCC No. 12078. The specification provides only examples of inducing apoptosis **in cell culture** by a single monoclonal antibody, mAb74, produced by hybridoma cell

line ATCC No. 12078, which had an "unexpected effect" of inducing apoptosis (see p. 4, lines 21-28 of the specification) and has a unique epitope that is distinct from epitopes recognized by other anti-HER2 antibodies (see p. 8, lines 26-36 to p. 9, lines 1-2 of the specification). The examples and support in the specification, as stated by Applicants on p. 15 of the Amendment filed February 2, 2006, verify that the specification only enables and exemplifies the induction of apoptosis **in cell culture** comprising administering mAb74, produced by hybridoma cell line ATCC No. 12078.

As stated in the Office Action mailed September 22, 2005, p. 10, Examiner notes that an "unexpected event is, by its nature, unpredictable". The unexpected nature of mAb74 indicates the antibody is novel and its properties regarding *in vivo* treatment of patients with cancer overexpressing HER2 are unknown and unpredictable because the specification states that the antibody's properties are unexpected, the specification does not provide guidance and examples for mAb74 or any antibody binding to HER2 to treat cancer by inducing apoptosis, and there is no relevant art teaching the treatment of cancer comprising administering an antibody that binds HER2 and induces apoptosis. It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less

information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the novel nature of the invention, the lack of adequate disclosure in the specification and lack of working examples for treatment of a HER2 overexpressing cancer in a patient, the breadth of the claims as drawn to any HER2 antibody, the quantity of experimentation necessary to determine if the broadly claimed antibody or antibody that binds to the same epitope as mAb74, produced by hybridoma cell line ATCC No. 12078 would successfully treat cancer in a patient, and given little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

5. Applicants argue that it is not undue experimentation for one skilled in the art to make antibodies to HER2 and select those with desired characteristics, i.e., antibodies that bind to HER2 and induce apoptosis in HER2 overexpressing cells (p. 15-16).

The argument has been considered but is not found persuasive because Applicants are excluding limitations recited in the claims regarding the treatment of HER2 overexpressing cancer in a patient. Applicants are not claiming the antibody alone. Applicants are enabled for monoclonal antibody mAb74 and antibodies that bind to the same epitope as mAb74, produced by hybridoma cell line ATCC No. 12078, which to bind HER2 and induce apoptosis in cells that are **in cell culture**, however,

Applicants are not enabled for these antibodies to treat cancer in a patient because the specification does not enable the treatment of patients with HER2 overexpressing cancer comprising administering these antibodies with an unexpected, unpredictable property, and one of skill in the art would be forced into undue experimentation to practice the claimed invention for the reasons set forth above.

6. Applicants argue that the *in vitro* cell culture assay used to screen for apoptosis-inducing antibodies that bind HER2 (Example 6 in specification), is an acceptable assay to extrapolate to *in vivo* treatment of HER2 overexpressing cancer because the cell types used in the assay (MCF7, MDA-MB-435, and SKBR3) mimic malignant human cells and are all members of a group of cell lines (referred to as the "NCI-60 Panel") that were developed by the National Cancer Institute for the explicit purpose of identifying compounds with anti-cancer activity. Applicants provided a reference, Voskoglou-Nomikos et al, Clinical Cancer Research 9:4227-4239 (2003), which correlates Phase II clinical trial results with cytotoxic drug studies done in cell culture. Applicants assert that the cell lines used in the present specification are suitable models for *in vivo* activity (p. 17-18).

The argument has been considered but not has been persuasive for the reasons set forth below. Voskoglou-Nomikos et al teach that the *in vitro* cell line model was predictive for breast and ovarian cancers under the compound oriented approach and that under the right framework and when panels are used, the *in vitro* cell line and human xenograft models **may** be useful in predicting the Phase II clinical trial

performance of cancer drugs (abstract). The Voskoglou-Nomikos et al teach the correlation of **cytotoxic drug** study results in cell culture to clinical trial results, of which none have a mechanism for binding to HER2 (Tables 1 and 2). Voskoglou-Nomikos et al does not teach the correlation of antibody therapy results in cell culture to clinical trials. Voskoglou-Nomikos et al teach that the *in vitro* cell line model **might be** predictive in the case of typical **cytotoxic cancer agents but might fail to provide reliable information for at least some of the noncytotoxic cancer drugs** (p. 4236, col. 1). Applicants' *in vitro* studies to screen for antibodies that bind HER2 and induce apoptosis were conducted only in MCF7 and MDA-MB-435 cells (Example 6). SKBR3 cells were not used in the apoptosis screen and are not on the list of 60 human cancer cell lines used in the screen and maintained by the National Cancer Institute (See Cell Lines in the *In Vitro* Screen, p. 1-3). Further, the cell line MDA-MB-435 has a disputed origin and studies provide convincing data that the cells are of melanoma origin (see Cell Lines in the *In Vitro* Screen, p. 2, and "MDA-MB-435: Breast or Melanoma Origin?"). Clearly, Voskoglou-Nomikos et al and the list of 60 human cancer cell lines used in the screen and maintained by the National Cancer Institute do not enable the extrapolation of *in vitro* results for the monoclonal antibody, mAB74, or any other HER2-binding antibody that induces apoptosis to cancer treatment or clinical trial results.

6. Applicants argue that the observations made in Drexler's study of Hodgkin and Reed-Sternberg cancer cell lines should not be applied to the particular cell lines used in the present specification. The cell lines used in the present specification to

demonstrate the induction of apoptosis by an antibody or fragment thereof that binds to HER2 are on the NCI-60 panel of cell lines that have been identified as particularly valuable for the identification of anti-cancer therapeutic molecules. None of the cell lines discussed in Drexler is on the NCI-60 Panel. Applicants assert that Voskoglou-Nomikos et al showed that anti-cancer results obtained using cell lines on the NCI-60 panel reasonable correlate to the results of Phase II clinical trials (p. 19).

The argument has been considered but is not found persuasive. The Drexler reference was provided as a relevant example of "acquisition or loss of certain properties during adaptation to culture systems". Dermer and Freshney (p. 11-12, Office action mailed September 22, 2005) also teach the loss of phenotypic characteristics in cultured cells associated with their normal counterpart and "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease, but were not addressed by Applicant. As stated in the Office action mailed September 22, 2005, on page 12, "Clearly it is well known in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions", hence one could not extrapolate the *in vitro* results of the specification to the treatment of cancer. As stated above, Voskoglou-Nomikos et teach the correlation between *in vitro* results and clinical trials for cytotoxic drugs and that the *in vitro* cell line model might be predictive in the case of typical cytotoxic cancer agents but might fail to provide reliable information for at least some of the noncytotoxic cancer drugs. As stated above, the only cell lines used in the apoptosis screen for antibodies were MCF7

and MDA-MB-435 cells, and the origin of MDA-MB-435 cells does not appear to be representative of breast tissue, as taught by the NCI-60 list (see Cell Lines in the *In Vitro* Screen, p. 2, and "MDA-MB-435: Breast or Melanoma Origin?"). Again, Voskoglou-Nomikos et al and the list of 60 human cancer cell lines used in the screen and maintained by the National Cancer Institute do not enable the extrapolation of *in vitro* results for the monoclonal antibody, mAB74, or any other HER2-binding antibody that induces apoptosis to cancer treatment or clinical trial results.

7. Applicants argue again that predictability alone is not the standard for enablement and refer to *In re Wands* for the standard of enablement. Applicants argue that Gura supports the reliance on the NCI panel of 60 human tumor cells to screen for anti-cancer drugs and supports that the *in vitro* results in the present application are a reasonable indication of the *in vivo* efficacy of the recited antibodies (p. 21).

This argument has been considered but has not been found persuasive. Gura teaches that the limitations of animal models has spurred the NCI to test drug candidates in cultures of human cells and now relies on 60 human tumor cell lines (p. 1042, col. 1), however, over the last 7 years (as of 1997), the NCI-60 panel has been used to screen almost 63,000 compounds, of which 5,000 exhibited tumor cell killing activity. Computer screening to identify agents with novel mechanisms of action allow those selected agents to go to clinical trials (p. 1042, col. 1). Gura teaches a method of screening anti-cancer drugs in human cell culture and identifying drugs that are of interest for clinical trials. Gura does not teach the correlation of *in vitro* results to clinical

trials, nor does Gura teach the enablement of treating a patient with HER2 overexpressing cancer by administering the mAb74 or any other HER2-binding antibody. Gura teaches the unpredictability of anti-cancer drug activity and the massive screening required to identify potential drug candidates, which exemplifies the unpredictable activity of novel anti-cancer drugs, such as the novel antibody, mAb74. As stated above, given the novel nature of the invention, the lack of adequate disclosure in the specification and lack of working examples for treatment of a HER2 overexpressing cancer in a patient, the breadth of the claims as drawn to any HER2 antibody, the quantity of experimentation necessary to determine if the broadly claimed antibody or antibody that binds to the same epitope as mAb74, produced by hybridoma cell line ATCC No. 12078 would successfully treat cancer in a patient, and given little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

8. Applicants argue that Jain focuses on the problems of chemical therapeutics and not antibody therapeutics and that Jain helps to support the conclusion that the present claims are enabled because Jain suggests that antibodies are able to reach the tumor effectively and would be appropriate as anti-tumor agents (p. 21).

The argument has been considered and has been found persuasive, in part, in that Jain supports the use of monoclonal antibodies for targeting solid tumors, however, Jain does not enable the claimed invention of treating HER2 overexpressing cancer in a patient comprising administering mAb74 or any antibody that binds HER2 and induces

apoptosis because Jain only teaches the advantage of antibodies in localizing to tumors and does not teach the successful treatment of cancer using the claimed antibodies or any related antibodies.

9. Applicants argue that Curti is not applicable to the enablement of the claims because Curti teaches tumor resistance to chemotherapeutic agents and not to antibody therapy (p. 22).

The argument has been considered and is found persuasive. Curti does not teach antibody therapy and does not relate to the enablement of the claims.

10. Applicants argue that the success of Herceptin, a successful monoclonal HER2 antibody for the treatment of HER2 overexpressing tumors, supports the Applicant's assertion that the present claims are enabled. Applicants argue that the question of whether some anti-HER2 antibodies accelerate tumor growth, as taught by Stansovski, fails to impact the enablement of the present claims.

The arguments have been considered but are not found persuasive because the success of Herceptin as a treatment of HER2-overexpressing cancer is an example of only one of many anti-HER2 antibodies in the art that was successful for treating cancer the clinical setting, which exemplifies the unpredictability of anti-HER2 antibodies in their ability to treat cancer. Stansovski, Lewis, and US Patent 5,677,171 exemplify the unexpected nature and function of HER-2 binding antibodies by teaching that some HER2 antibodies actually accelerate tumor growth and that not every HER2

antibody can be used to effectively treat cancer as Herceptin (see the Office Action mailed September 22, 2005, p. 15). The art teaches that HER2 antibodies have different and sometimes unexpected functions, and it cannot be predicted which ones will effectively treat cancer. The specification discloses that mAb74 has the unexpected result of inducing apoptosis. Because of the novel nature of this monoclonal antibody in cell culture and its unknown therapeutic effects *in vivo*, given the art teaches that HER2 antibodies have unexpected functions and do not all effectively treat cancer, the lack of adequate disclosure in the specification and lack of working examples for treatment of a HER2 overexpressing cancer in a patient, the breadth of the claims as drawn to any HER2 antibody, the quantity of experimentation necessary to determine if the broadly claimed antibody or antibody that binds to the same epitope as mAb74, produced by hybridoma cell line ATCC No. 12078 would successfully treat cancer in a patient, and given little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

11. Applicants argue that using the teachings in the specification and the knowledge in the art, one skilled in the art could select an antibody or fragment thereof that binds HER2 and induces apoptosis in HER overexpressing cells without undue experimentation. Discarding some undesirable antibodies in the selection process is simply a part of the experimentation permitted by *Wands* (p. 23-24).

The argument has been considered but is not found persuasive because Applicants are excluding limitations recited in the claims regarding the treatment of

HER2 overexpressing cancer in a patient. Applicants are not claiming the antibody alone. Applicants do not provide guidance or examples for administering and discarding antibodies that do not effectively treat patients with HER2 overexpressing cancer. Applicants are enabled for monoclonal antibody mAb74 and antibodies that bind to the same epitope as mAb74, produced by hybridoma cell line ATCC No. 12078, which to bind HER2 and induce apoptosis in cells that are **in cell culture**, however, Applicants are not enabled for these antibodies to treat cancer in a patient because the specification does not enable the treatment of patients with HER2 overexpressing cancer comprising administering these antibodies with an unexpected, unpredictable property, and one of skill in the art would be forced into undue experimentation to practice the claimed invention for the reasons set forth above.

12. Applicants argue that Strobel has no bearing on whether the present claims are enabled (p. 24).

This argument has been considered and is not found persuasive because Strobel teaches that although antibodies may share the same binding properties, they may not share the same function or activity that would effectively inhibit malignancy (p. 15 of the Office Action mailed September 22, 2005). The Strobel reference is relevant because it teaches that although antibodies share the same binding properties, they may not predictably both share the same function, for example, the function of treating a patient with cancer. Although an antibody may share the same binding and apoptotic activity as novel mAb74, it would not be predicted that it could treat a patient with HER2

overexpressing cancer. The claimed method of treating cancer characterized by overexpression of HER2 is not enabled for the reasons set forth above in accordance with *In re Wands*.

13. All other rejections recited in the Office Action mailed September 22, 2005 are hereby withdrawn.

14. **Conclusion:** No claim is allowed. The closest art appears to be US Patent 5,910,486, Curiel et al, issued 6/8/99 and filed 6/6/95. US Patent 5,910,486 teaches **intracellular expression of** a HER2 antibody that induces apoptosis in HER2-overexpressing tumor cells (Example 6), however, US Patent 5,910,486 does not teach a method for treating cancer characterized by overexpression of HER2 **in a patient** comprising **administering** said HER2 antibody that induces apoptosis.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. ' 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. ' 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY

PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 8:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Laura B Goddard, Ph.D.
Examiner
Art Unit 1642

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER